Remarks

Entry of the amendment is respectfully requested. The amendment reflects an earnest effort to advance prosecution and respond to points raised for the first time in the Final rejection.

Upon entry of the amendment claims 3-7 and 10-23 are pending. Claims 3-5 have been amended to include a patient selection step and a duration of treatment to achieve stabilization (no change) or improvement of a cognitive function as evidenced by Table 2 or figure 1. Reference to MMSE in the claims is limited to defining the treated patient population. Note especially claims 14-17 and 22-23, as amended. Support for the cognitive function variables and manners of measuring is found in the specification, in particular consider the material starting on page six of the specification. Additionally, house keeping amendments were made to the remaining claims with the exception of claims 10, 13 and 18, where no amendments were made.

Rejection under 35 U.S.C § 112

Claims 14-17 and 22-23 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. Applicants respectfully traverse.

The claims have been amended to address the issues raised in the Official Action. The cancellation and amendments were done solely to advance prosecution. Four patient evaluations tests are mentioned in the specification: Mini-Mental State Examination (MMSE): Clinician's Interview-Based Impression of Change plus (CIBIC plus): Severe Impairment Battery (SIB); and Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-COG). (Applicants note that a fifth test discussed in the specification, the Cochran-Mantel-Haenszel test, is not used to evaluate patients but rather to analyze of the evaluation method.) The MMSE test values are used to defined the condition of the patient in terms of the severity of the Alzheimer's Disease (AD) condition. The MMSE test is administered to the patient. The Clinician's Interview-Based Impression of Change plus test is employed to measure cognitive functioning. In CIBIC plus test, a patient's guardian or family is interviewed and then the patient. A SIB evaluation is a method of evaluating severely impaired cognitive function which relies on patient interviews. Figure 1 shows the results of SIB evaluation of severe AD patients. ADAS-cog, a test used for mild and moderate AD patients, is mentioned in the specification as not being suitable with

severe AD patients because of the complexity of the questions employed. Table 2 shows the results of a method of CIBIC plus evaluation of severe AD patients. The patients to be treated by the claimed method are those having MMSE scores between 5 and 9. The assessment of the progress of these patients undergoing the claimed therapy is based on the CIBIC plus values. Administration of the placebo shows that the condition of the "untreated" patients deteriorates. The E2020 group shows various degrees of improvement or stabilization (i.e., no deterioration) in condition. See Figure 1 and Table 2.

Some confusion may have arisen relative to the use of MMSE values to define the patient population, the manner in which the patient is assessed during treatment and the claim format. MMSE values were not intended to be used for both patient population characterization and patient assessment purposes in the claims. This possible confusion may have prompted the instant rejection. The claims as amended are clearly directed to the treatment of the specified patient population, characterized by MMSE criteria, with donepezil, e.g. Group E2020 and the progress of treatment is measured relative to a cognitive function. In light of the amendment, withdrawal of the rejection is respectfully requested.

Rejection under 35 USC § 102

Claims 3-7 and 10-23 are rejected under 35 USC § 102 over Feldman et al. Applicants respectfully traverse.

The claims, as amended, require a selection of a patient population selection having severe AD as defined by MMSE values and then administration of donepezil. In addition the claims, require a duration of the treatment regimen be sufficient to improve or stabilize (no change) the patient' condition in terms of a cognitive function.

Feldman et al are silent as to the selection step, the specified more limited patient type and the outcome for the treatment regimen. Further, a person of ordinary skill in the art (POSITA) would understand the Feldman reference to provide no information about the performance of sever AD patients per se, but rather only for the performance of the group as a whole (the data are not sorted vs., severity of the disease.) Significantly, the means MMSE score for the study group is nearly 3 points above the currently claimed range. Feldman does report at least one study patient with an MMSE of 5 (range is reported as 5-17). However, Feldman does

not provide any indication as to whether, e.g. the improvement/stabilization of the mean cognitive scores of the treatment group reflects the experience of the entire study population, or only by, e.g. AD patients having MMSE of 10+. In this regard, it may be instructive that Feldman actually closes by stating that "{a} confirmatory study is currently being undertaken in patients with severe AD." This would suggest to POSITA that the with respect to severe AD patients were, at best, equivocal, else the need for a confirmatory study would not have been alluded to.

For there to be anticipation a reference must teach each and every element required by the claim. This the reference fails to do. Withdrawal of the rejection is respectfully requested.

Rejections under 35 USC § 103

Claims 3-7 and 10-23 are rejected under 35 U.S.C. § 103(a) as being unpatentable over U.S. Patent No. 5,100,901 ('901 Patent). Applicants respectfully traverse.

Applicants respectfully traverse the rejection and respectfully submit that the '901 patent does not disclose, suggest, or provide a reasonable expectation of success for administering donepezil to patients with severe Alzheimer's dementia having a Mini-Mental State Examination score of 5 to 9.

As amended the claims require (i) selecting specific patients having Mini-Mental State Examination score of 5 to 9, and (ii) administering donepezil to said patients for a sufficient period of time as to stabilize (no change) or improve a cognitive function. Such is not evident form the teaching of the '901 patent.

As described in the specification of the pending application, the pathology of mild and moderate Alzheimer's dementia is completely different from the pathology of severe Alzheimer's dementia.[1] Mild and moderate Alzheimer's dementia is characterized by a generalized atrophy of the brain, the appearance of senile plaques of the cerebral cortex, change to neurofibrils, abnormalities in cholinergic neurons, and a decrease in acetylcholine.[2] Severe Alzheimer's dementia is characterized by a loss of neural structure within the brain, a marked drop in brain

[1] Specification at page 2, lines 8-9.
[2] Specification at page 1, lines 16-22.

volume, and a significant decrease in blood flow within the brain.[3] Moreover, the Alzheimer's Disease Assessment Scale, cognitive subscale (ADAS-cog) that is used to diagnosis and evaluate mild and moderate Alzheimer's dementia cannot be used to diagnosis and evaluate severe Alzheimer's dementia.[4]

The '901 patent discusses compounds, such as donepezil, that are acetylcholinesterase inhibitors. It was discovered that donepezil was useful for treating mild and moderate Alzheimer's dementia; however, it would not be expected that donepezil would be useful for treating severe Alzheimer's dementia because severe Alzheimer's dementia has a different pathology than mild/moderate Alzheimer's dementia. For example, it would not be expected that donepezil, which is useful for treating a disease characterized by abnormalities in cholinergic neurons and/or a decrease in acetylcholine (i.e., mild/moderate Alzheimer's dementia), would also be useful for treating a disease characterized by a loss of neural structure within the brain (i.e., severe Alzheimer's dementia). If there is a loss of neural structure, it would not be expected that an acetylcholinesterase inhibitor, i.e., donepezil, would be a successful treatment.

The Examiner urges on page16 of the Office Action that one of ordinary skill would expect that neural changes characteristic of mild and moderate Alzheimer's disease do not disappear in severe Alzheimer's dementia ("AD"). There is no evidentiary support offered for this proposition. Examiner further supposes that other traits associated with severe AD are additive and separately treatable. No evidentiary support is offered for this view. This appears to be mere supposition and should be withdrawn as support for a finding of obviousness.

In view of the fact that the '901 patent discloses compounds having mechanisms of action that would be useful for treating mild/moderate Alzheimer's dementia and not severe Alzheimer's dementia (i.e., in view of the different pathologies of the diseases), one skilled in the art would not have a reasonable expectation that donepezil would be useful for treating severe Alzheimer's dementia.

In view thereof, the pending claims are unobvious over the specifications and claims of the '901 patent. Applicants respectfully request that the rejections be withdrawn.

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[3] Specification at page 2, lines 5-9.
[4] Specification at page 2, line 11 to page 3, line 2.

Claims 3-7 and 10-23 are rejected under 35 U.S.C. § 103 as being obvious over US Patent No. 4,895,841 ('841 Patent). Applicants respectfully traverse.

Applicants respectfully traverse the rejections and respectfully submit that the teaching of the '841 patent is duplicative of that of the '901 patent discussed above. The deficiencies of the prima facie case note above are also applicable here. The reference does not disclose, suggest, or provide a reasonable expectation of success for administering donepezil to patients with severe Alzheimer's dementia associated with a Mini-Mental State Examination score of 5 to 9. A proper prima facie case has not been established. Withdrawal of the rejection is respectfully requested.

Rejections under Obviousness-Type Double Patenting

Claims 3-7 and 10-23 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 9 and 10 of U.S. Patent No. 5,100,901. Applicants respectfully traverse.

The claims have been amended to maintain a clear line of demarcation between the claims of the instant application as those of the patent. Please note that the patient populations, as claimed are distinct, the active ingredient claimed herein, donepezil, is merely embraced by the family of compounds identified in the claims of the patent, and the regimen required by the instant claims is not evident in the claims of the patent.

Claims 9 and 10 are method claims which depend on claim 8. Claim 8 incorporates the compound subject matter of claim 1. Claim 8 is directed to a method for treating a disease accompanied by acetylcholinesterase activity by administering to a human patient an effective amount of the cyclic amine compound as defined in claim 1 or a pharmacologically acceptable salt thereof for inhibiting the acetylcholinesterase activity. Claims 9 and 10 further define the diseased condition as senile dementia and the senile dementia as being of the Alzheimer type, respectively.

In an obviousness type double patenting rejection, the claims are relied for their teachings and not the specification of the patent. Here, there is no guidance provided by the claims, alone, which are suggestive of the differences note above. There are no secondary references relied

upon for the missing teachings. A proper prima facie case has not been established. Withdrawal of the rejection is respectfully requested.

Claims 3-7 and 10-23 are rejected under the judicially created doctrine of obviousness-type double patenting over claims 12 and 13 of U.S. Patent No. 4,895,841. Applicants respectfully traverse.

Applicants urge that the claims as amended maintain a clear line of demarcation with those identified by the Examiner. Please note that the patient populations, as claimed are distinct, the active ingredient claimed herein, donepezil, is merely embraced by the family of compounds identified in the claims of the patent, and the regimen required by the instant claims is not evident in the claims of the patent.

Claims 12 and 13 of the patent are method claims which depend on claim 11. Claim 11 incorporates the compound subject matter of claim 1 of the patent.

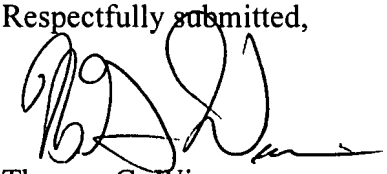
Claim 11 is directed to a method for treating a disease caused by acetylcholinesterase activity which entails administering to a human patient having the disease, an effective amount of the cyclic amine compound as defined in claim 1, or a pharmacologically acceptable salt thereof. Claims 12 and 13 specify the disease condition as senile dementia and the dementia as being of the Alzheimer type, respectively.

In an obviousness type double patenting rejection, the claims are relied for their teachings and not the specification of the patent. Here, there is no guidance provided by the claims, alone, which are suggestive of the differences note above. There are no secondary references relied upon for the missing teachings. A proper prima facie case has not been established. Withdrawal of the rejection is respectfully requested.

Conclusion

An early and favorable reconsideration and allowance of claims 3-7 and 10-23 is respectfully requested. The Examiner is encouraged to contact the undersigned to expedite prosecution of this application.

Respectfully submitted,



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